CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.1219739

Available online at: http://www.iajps.com Research Article

FORMULATION AND EVALUATION OF TIME DEPENDENDT RELEASE OF MONTELUKAST TABLETS BY USING MINI TABLET TECHNOLOGY

Faizan Sayeed*

Mesco College of Pharmacy, Karwan Road, Mustaidpura, Hyderabad, Telangana 500006

Abstract:

Montelukast is a leukotriene receptor antagonist (LTRA) used for the maintenance treatment of asthma, chronic asthma attacks and to relive symptoms of seasonal allergies. The main drawback of conventional Montelukast formulation is that it undergoes hepatic first pass metabolism. Thus, it shows plasma or biological half-life 2.5 to 5.5 hrs, thereby decreasing bioavailability upto 64%. The present work describes such delivery system, which will improve the biological half-life as well as bioavailability of Montelukast. This makes Montelukast a suitable candidate for incorporation in sustained-release dosage form and was used as a model drug. Thus the present investigation was aimed to develop timed release tablets of Montelukast sodium by compression coating using enteric coated polymers like Eudragit L-100 and S-100 to resist from acidic pH and prevent gastric irritation.

The pre-compressional parameters such as angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio for the physical mixtures of the formulations were evaluated and the results were within the limits. The prepared core and compression-coated tablets were studied for their physical properties like weight variation, hardness, friability and drug content uniformity using reported procedure. All the post compressional parameters were within the limits.

The FTIR studies were done for drug-excipient compatibility. The infra-red spectrum for pure drug and Montelukast sodium formulation. The following principal peaks were observed from the FT-IR spectral analysis.

- *O-H stretching seen in alcohols -- 3212.619 cm-1*
- *C=C stretching of the benzene ring -- 1453.85 cm-1*
- *C-H bend -- 1589.97cm-1*

Calibration curves were constructed for Montelukast sodium in pH 1.2, 6.8 and 7.4 buffers with concentration ranging from 5 - 40 µg/mL against absorbance at 332nm using UV spectrophotometer. The present analytical method obeyed Beer's law within the concentration range and plots showed good linearity.

In vitro drug dissolution studies were carried out in pH 1.2 for 2 hrs, pH 6.8 for 4 hrs and pH 7.4 phosphate buffer for 8 hrs respectively and based on the in vitro drug release profiles, formulations F1, F2, F4, F5 and F7 has passed the criteria of Q NLT < 80% within 30 minutes of exposure in pH 7.4 phosphate buffer.

Keywords: *Montelukast, timed release tablets, pre-compressional parameters, enteric coated polymers.*

Corresponding author:

Faizan Sayeed,
Vice Principal,
Mesco College of Pharmacy,
Karwan Road, Mustaidpura,
Hyderabad,
Telangana 500006.

QR code

Please cite this article in press Faizan Sayeed ., ***Formulation and Evaluation of Time Dependendt Release of Montelukast Tablets by Using Mini Tablet Technology,*** *Indo Am. J. P. Sci, 2018; 05(04).*

INTRODUCTION:

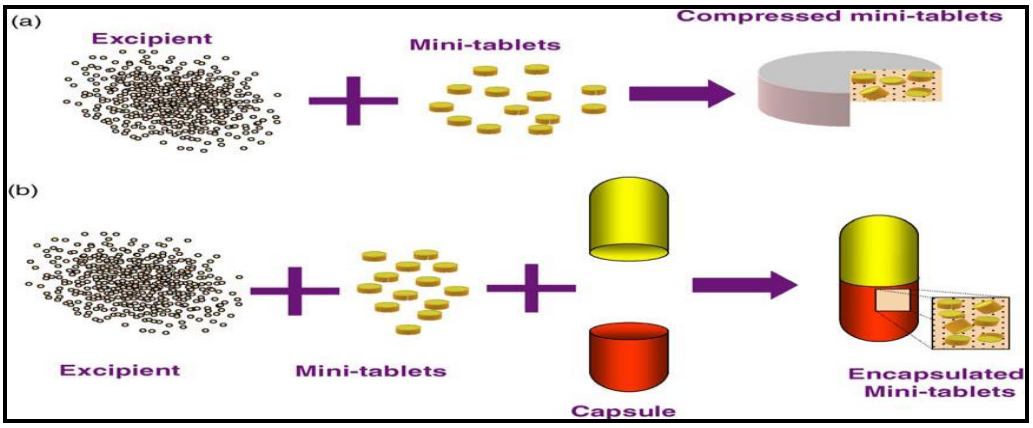
Circadian rhythms are self-sustaining, endogenous oscillations that occur with a periodicity of about 24 hrs. Normally circadian rhythms are synchronized according to internal biological clocks related to the sleep-wake cycle. Our circadian rhythm is based on sleep-activity cycle and is influenced by our genetic makeup and thereby affects our body's function throughout day and night (24 hrs period). Circadian rhythm regulates many body functions in human like metabolism, physiology, behavior, sleep pattern, hormone production. There are number of conditions which show circadian pattern and advantage could be taken by timing and adjusting the administration of drugs according to the circadian rhythm of the disease. Diseases such as cardiovascular, asthma, peptic ulcer, arthritis etc., follow the body's circadian rhythm. Co-ordination of biological rhythms and medical treatment is called chronotherapy while chronotherapeutics is the discipline concerned with the delivery of drugs according to inherent activities of a disease over a certain period of time. The potential benefits of chronotherapeutics have been demonstrated in the management of a number of diseases. In particular there is a great deal of interest in how chronotherapy can particularly benefit patients suffering from allergic rhinitis, rheumatoid arthritis and related disorders, asthma, cancer, cardiovascular diseases and peptic ulcer disease[1-3].

Asthma is a chronic inflammatory disease of the airways, characterized by hyper responsiveness to a variety of stimuli. The role of circadian rhythms in the pathogenesis and treatment of asthma indicates that airway resistance increases progressively at night in asthmatic patients. Circadian changes are seen in normal lung function, which reaches a low point in the early morning hrs. The worsening of asthma at night commonly referred to as Nocturnal asthma (NA). A drug delivery system administered at bed time but releasing drug during morning hours would be ideal in this case[1, 2].

The montelukast is a leukotrine receptor antagonist (LTRA) used for the maintenance treatment of asthma, chronic asthma attacks and to relive symptoms of seasonal allergies[4-6]. The main drawback of conventional montelukast formulation is that it undergoes hepatic first pass metabolism. Thus, it shows plasma or biological half-life 2.5 to 5.5 hrs[7], there by decreasing bioavailability upto 64%[8]. The present work describes such delivery system, which will improve the biological half-life as well as bioavailability of montelukast. This makes montelukast a suitable drug candidate for incorporation in sustained-release dosage form and was used as a model drug.

During the last two decades there has been remarkable increase in interest in sustained release drug delivery system. Such dosage forms are designed to release a drug at a predetermined rate by maintaining a constant drug level for a specific period of time with minimum side effects. There are several advantages of sustained-release drug delivery over conventional dosage forms like improved patient compliance due to less frequent drug administration, reduction of fluctuations in steady-state drug levels, maximum utilization of the drug, increased safety margin of potent drug, reduction in healthcare costs through improved therapy, shorter treatment period and less frequency of dosing. SR products are designed to bring the blood level of a drug immediately to therapeutic concentrations by means of an initial dose pattern and then sustain this level for a certain predetermined time with the maintenance portion. The principle goal of SR dosage forms is the improvement of drug therapy assessed by the relationship between advantages and disadvantages of the use of SR systems. Such a release pattern is known as "sustained release" [9,10].
Oral controlled release drug delivery systems can be classified into two broad groups: Single unit dosage forms (SUDFs), such as tablets or capsules and multiple unit dosage forms (MUDFs), such as granules, pellets or mini-tablets. The concept of MUDFs was initially introduced in the early 1950's. The production of MUDFs is a common strategy to control the release of a drug as shown by reproducibility of the release profiles when compared to the ones obtained with SUDFs. The concept of MUDFs is characterized by the fact that the dose is administered as a number of subunits, each one containing the drug. The dose is then the sum of the quantity of drug in each subunit and the functionality of the entire dose is directly correlated to the individual subunits.

Like other MUDFs several mini-tablets can be filled into either hard capsules or compacted into bigger tablets that, after disintegration, release these subunits as multiple dosage forms[11].



Mini-tablets delivered as a tablet (a) or a capsule (b).

This concept was used to produce a coated mini-tablets-in-capsule system device combining immediate-release and sustained release coated mini-tablets. This system can produce a rapid rise in plasmatic concentrations of some drugs that are requested to promptly excise the therapeutic effect followed by an extended release phase in order to avoid repeated administration. The coated mini-tablets-in-capsule system were able to deliver a first fraction of the dose in a very short time and to deliver a second fraction for a longer period of time at a constant rate. Moreover, the flexibility of the dosage regimen was also studied by the combination of different number of mini-tablets as sustained release and different dose of the drug in the immediate-release.

Coated oral SR forms of drugs are widely used to improve drug tolerance or to yield dosing regimen that is to easier to manage for patients. However, production of a SR dosage form that would maintain an effective plasma montelukast sodium concentration would improve patient compliance. The purpose of this thesis was to optimize a prolonged-release montelukast sodium dosage form using coated mini-tablets-in-capsule system containing coated mini-tablets. This thesis aimed to reduce the size of the montelukast sodium tablet such that it could be enclosed in a capsule, and then deploy mini-tablets with different release properties within the one coated mini-tablets-in-capsule system [12, 13].

METHODOLOGY:

Preparation of stock solution

10 mg of MONTELUKAST SODIUM was dissolved in 10 mL of methanol in 10 mL volumetric flask and made up to volume with methanol.

pH	Volume of NaOH (mL)
6.8	224
7.4	391

Construction of Calibration curve

For the estimation of MONTELUKAST SODIUM, the stock solution was subsequently diluted with subsequent medium to get a series of dilutions containing 5, 10, 20, 30, 40µg/mL of solution and measured the absorbance at 332 nm (UV-VIS spectrophotometer, SL-150, Elico) against same dilution as blank. The absorbance was plotted against concentration of MONTELUKAST SODIUM as shown in results and discussion.

Preparation of buffers:

Calibration curve for MONTELUKAST SODIUM was constructed in different buffer solutions as the solubility studies were carried out for the drug in all these buffers in the later stages.

They include

1. 1.2 pH buffer
2. 6.8 Phosphate buffer
3. 7.4 Phosphate buffer

Preparation of buffers (formula per litre)

1.2 pH buffer

8.5mL of concentrated Hydrochloric acid was diluted with distilled water and volume was adjusted to 1000mL.

6.8 And 7.4 pH Phosphate buffer

250mL of 0.2M potassium dihydrogen phosphate was added with required volume of 0.2M sodium hydroxide solution and the volume was adjusted to 1000mL.

Volume of NaOH added to each pH buffer

Calibration curve of Montelukast sodium in 1.2 pH buffer

The present analytical method obeyed Beer's law in the concentration range of 5-40µg/mL and is suitable for the estimation of MONTELUKAST SODIUM. The value of R^2 (correlation coefficient) for the linear

regression equation was found to be 1. The linear regression equation for the calibration curve is as follows:
y = 0.021x+3E-05

Calibration curve of Montelukast sodium in 6.8pH buffer:
The present analytical method obeyed Beer's law in the concentration range of 5-40µg/mL and is suitable for the estimation of MONTELUKAST SODIUM. The value of R^2 (correlation coefficient) for the linear regression equation was found to be 0.999. The linear regression equation for the calibration curve is as follows:
y = 0.022x+0.005

Calibration curve of Montelukast sodium in 7.4pH buffer:
The present analytical method obeyed Beer's law in the concentration range of 5-40µg/mL and is suitable for the estimation of MONTELUKAST SODIUM. The value of R^2 (correlation coefficient) for the linear regression equation was found to be 0.999. The linear regression equation for the calibration curve is as follows:
y = 0.013x+0.002

Solubility determination:
Excess of MONTELUKAST SODIUM was added to 5ml of each fluid in a 25 ml stoppered conical flasks and the mixtures were shaken for 24 hours at room temperature (25±1°C) on a rotary flask shaker. After 24 hours of shaking 1 mL aliquots were withdrawn and filtered immediately using a 0.45µ nylon disc filter. The filtered samples were diluted suitably and assayed for MONTELUKAST SODIUM by measuring absorbance at 332 nm. Shaking was continued until three consecutive estimations were same. The solubility experiments were run in triplicate.

Characterization of binary systems by FTIR spectroscopy:
FTIR spectra were obtained on spectrum 100 FTIR (Perkin-Elmer). Samples were prepared in KBr disks and data were collected over a spectral region from 4000 to 400 cm^{-1}.

Preparation and Evaluation of Montelukast Sodium Timed Release Tablets
In the present investigation timed release tablets of MONTELUKAST SODIUM were prepared using different rate controlling polymers by wet granulation method and evaluated for drug content, uniformity of weight, hardness, friability and dissolution properties.

Preparation of tablets
Wet granulation method (preparation of core tablet):
Montelukast sodium, lactose, maize starch, plasdone k 30, sodium starch glycolate, colloidal silicon dioxide were mixed well and passed through the sieve no 30 and moistened with water to form a damp mass. The damp mass was passed through sieve no 8 to obtain granules. The granules thus obtained were dried at 60^0 c till LOD of <2.5% w/w was achieved. The dried granules were sieved through sieve no 20 and lubricated with magnesium stearate. The granules were compressed by employing 8 mm punch.

Preparation of compression-coated tablets:
The formulated core tablets were compression-coated with the different coatings of Eudragit L-100 and S-100 in different ratios along with HPMC. For compression coating, about 50 % of coating system was first placed in the die cavity. Then, the core tablet was carefully positioned at the centre manually and pre-compressed. Then the balance 50% of the coating system was placed on the pre-compressed tablet and the tablet was pressed using the 12 mm punch compressed on a single punch tablet machine (Cadmach, India).

Preformulation studies:
Preformulation testing is the first step in the rational development of the dosage forms. It can be defined as an investigation of physical and chemical properties of a drug substance alone and combined with excipients. The objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms that can be mass produced.

The following preformulation studies were performed on Montelukast Sodium API:

Determination of densities:
Apparent density (bulk): Bulk density is the ratio of given mass of powder to its bulk volume. The bulk density, as a measure used to describe packing materials or granules, was determined transferring the accurately weighed amount of powder sample to the graduated cylinder with the aid of a funnel. The powder was leveled carefully without compacting and the unsettled apparent volume (Vo) was noted. The bulk density in g/mL was calculated by the formula:

Bulk density = M/Vo Where M is the weight of the sample taken

Tapped density:
After noting down the volume (Vo) in bulk density testing, the graduated cylinder was tapped mechanically using a suitable tapped density tester that provides a fixed tap of 14±2mm at 300 drops per minute, for 500 times initially and the tapped volume(Va) was measured to the nearest graduated unit. The tapping was repeated for an additional 750 times and the tapped volume (Vb) was measured to the nearest graduated unit. If the difference between the two measurements is less than 2%, Vb is the final tapped volume (Vf). If the difference is greater than 2%, the tapping was repeated at the increments of 1250 taps until the difference between the two successive measurements is less than 2%.

The tapped density, in g/mL was calculated by the formula
Tapped density = M/Vf, Where M is the sample taken for bulk density testing

Carr's index (compressibility):
The compressibility and Hausner's ratio are the measures of the propensity of a powder to be compressed. As such, these are the measures of relative importance of inter particulate interaction. In a free flowing powder, such interactions are of less significant and the bulk and tapped densities will be closer in value. For poor flowing materials, the bulk and tapped densities will be observed. These differences are reflected in the compressibility index and the Hausner's ratio. Based on the apparent bulk density and tapped density, the percentage compressibility of the bulk drug was determined by using the following formula

$$\% \text{ compressibility} = \frac{\text{tapped density- bulk density}}{\text{Tapped density}} * 100$$

Hausner's ratio:
The ratio of tapped density to the bulk density of the powders is called the Hausner's ratio.

$$\text{Hausner's ratio} = \frac{\text{tapped density}}{\text{Bulk density}}$$

EVALUATION OF COMPRESSED COATED TABLETS:
Drug content:
The core and compression-coated tablets were tested for their drug content. The 10 tablets were finely powdered and quantity of the powder equivalent to 160 mg of Montelukast sodium was accurately weighed and transferred to 100 ml volumetric flasks containing 50 ml of pH7.4 Phosphate buffer and allowed to stand for 10 hrs with intermittent shaking. The solution was made up to 100 ml with pH 7.4 phosphate buffer. The solutions were filtered and drug content was estimated using UV-spectrophotometer (Elico SL-150) at 332 nm. The estimations were carried out in triplicate and the results were reported in the Table no:9

Hardness:
Six tablets from each batch were selected and hardness was measured using Monsanto hardness tester (M/s Campbell Electronics, MODEL EIC-66, India). The results were given in Table no: 9

Friability (%F):
Ten tablets from each batch were selected randomly and weighed. These pre weighed tablets were subjected to friability testing using Roche friabilator (M/s Campbell Electronics, India) for 100 revolutions. The tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at height of 6 inches in each revolution. Tablets were removed, de-dusted and weighed again. Following formula was used to calculate the friability. The results were given in Table no:9.

%F =1-(loss in weight/ initial weight)* 100

Weight variation
Weight variation was calculated as per method described in USP. 20 tablets were weighed individually and the average weight is calculated. The requirements are met if the weights of not more than 2 of tablets differ by more than the percentage listed in table below and no tablets differ in weight by more than double that percentage. The results were given in table no:9.
Weight variations allowed as USPXX- NF XV

Average weight of tablet (mg)	Percentage difference allowed
≤130	10
130-324	7.5
>324	5

***In vitro* dissolution studies**

The Susceptibility of the matrix tablets of Montelukast sodium to remain intact and the release of the active ingredient in the physiological environment of stomach, small intestine and colon was assessed by conducting in vitro drug release studies under conditions mimicking mouth to colon. This study was carried out using USP dissolution test apparatus- II at 50rpm and 37±0.5^{0}c by using in situ pH change method. The tablets were tested for drug release in 500ml 1.2 pH buffer for first 2hrs as average gastric emptying time was estimated as 2hrs. A sample of 5ml of the dissolution medium was withdrawn after 2hrs to determine the drug release. The amount of drug release was analyzed by UV spectrophotometer at 332 nm. In the dissolution media 245 ml of 0.09 M $Na_3PO_4 \cdot 12\ H_2O$ was added to get pH of 6.8 and dissolution was conducted for the next 4 hrs dissolution. 5 mL of sample aliquots were withdrawn at specific time intervals and diluted with respective buffer to determine the drug release. Finally the dissolution medium was adjusted to 7.4 pH by adding 87 ml of 0.09 M Na3PO4·12 H2O was added to get pH 7.4 for the remaining 8 hrs.5 mL of sample aliquots were withdrawn at specific time intervals and the amount of drug release was analyzed by UV spectrophotometer at max wavelength of 332nm. Percent of Montelukast sodium dissolved at different time intervals and various dissolution parameters were obtained in the results.

RESULTS:

Table 1: Calibration curve data for the estimation of MONTELUKAST SODIUM in 1.2 pH buffer

CONCENTRATION(µg/mL)	ABSORBANCE
5	0.108
10	0.213
20	0.426
30	0.635
40	0.847

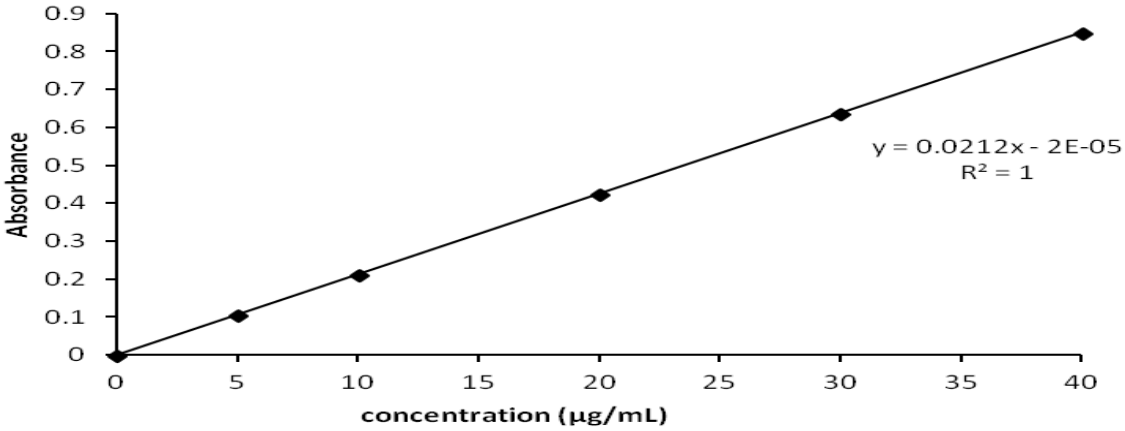


Fig.1: Calibration curve of MONTELUKAST SODIUM in 1.2 pH buffer

Table 2: Calibration curve data for the estimation of MONTELUKAST SODIUM in 6.8pH buffer

CONCENTRATION(µg/mL)	ABSORBANCE
5	0.125
10	0.234
20	0.444
30	0.654
40	0.867

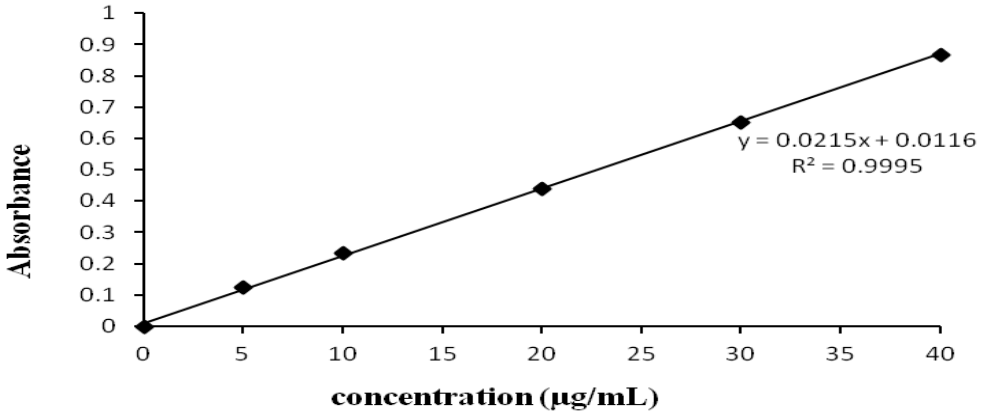


Fig.2: Calibration curve of MONTELUKAST SODIUM in 6.8pH buffer

Table 3: Calibration curve data for the estimation of MONTELUKAST SODIUM in 7.4 pH buffer

CONCENTRATION(µg/mL)	ABSORBANCE
5	0.074
10	0.142
20	0.272
30	0.413
40	0.556

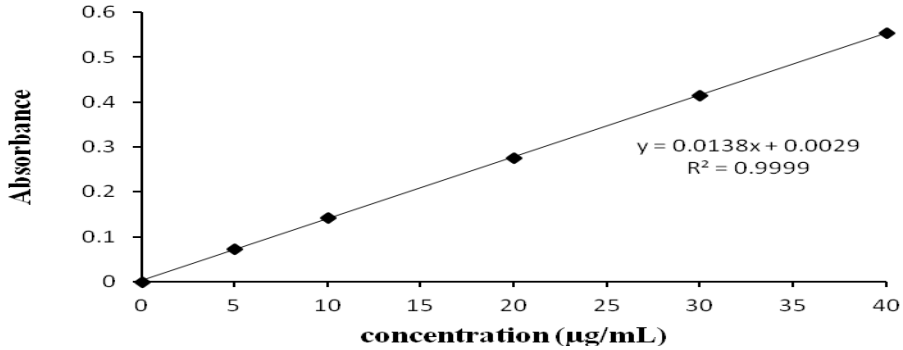


Fig.3: Calibration curve for MONTELUKAST SODIUM in 7.4 pH buffer

Table 4: Solubility determination of Montelukast sodium

MEDIA	SOLUBILITY(mg/mL)
Distilled water	0.0511
1.2 p^H	1
6.8 p^H	5
7.4 p^H	15

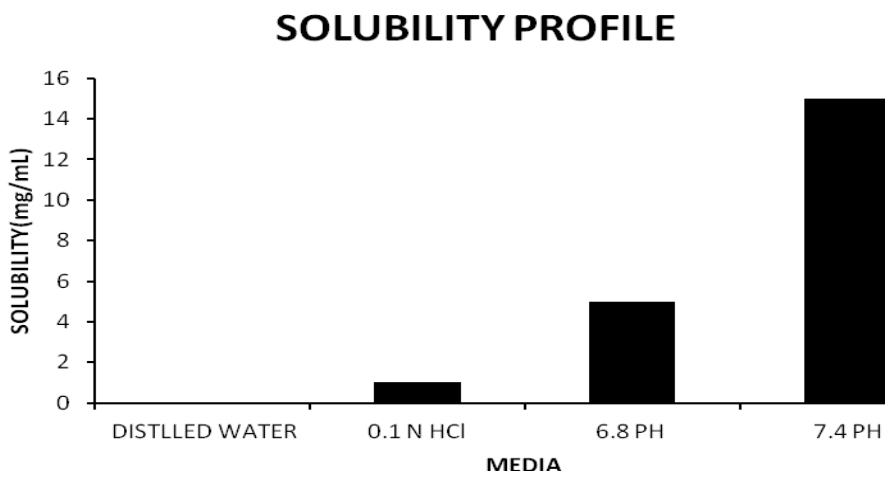


Fig.4: Solubility studies of MONTELUKAST SODIUM in different media

FTIR STUDIES:

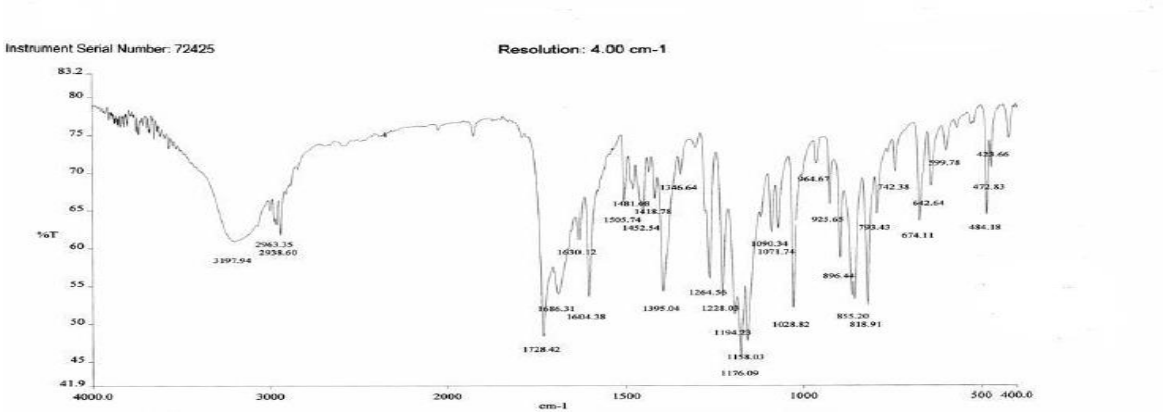


Fig.5: FTIR Spectrum for Montelukast sodium pure drug

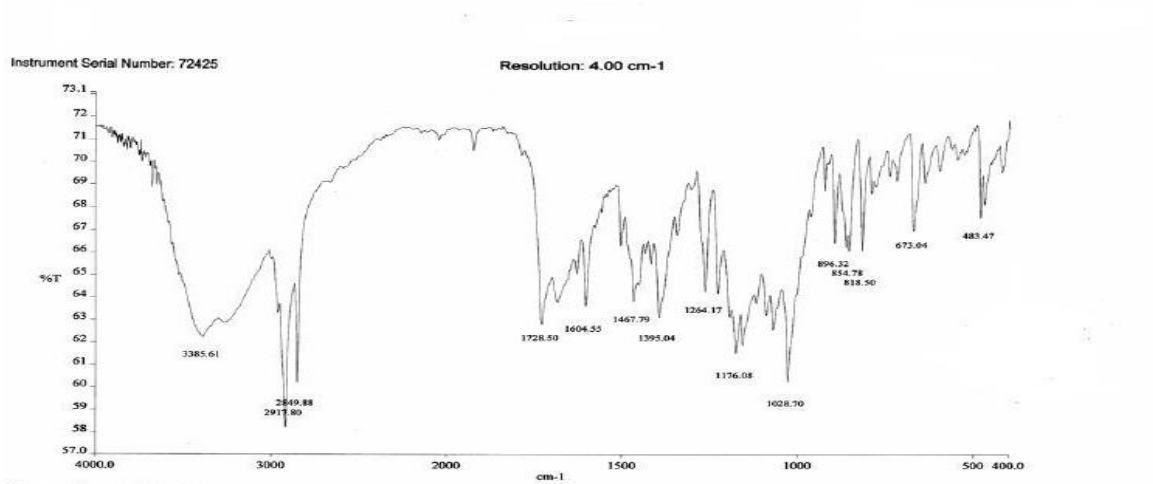


Fig.6:.FTIR spectrum of Montelukast sodium formulation

Table 5: Formulation

INGREDIENTS	QUANTITY PER TABLET IN mg
Montelukast sodium	100
Lactose monohydrate	40
Maize starch	11.4
Plasadone K 30	3
Sodium starch glycollate	3
Colloidal silicon dioxide	1
Magnesium stearate	1.6

Total weight of tablet= 160 mg

Table 6: Preparation of compression-coated tablets

FORMULATION INGREDIENTS(mg/tab)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Eudragit L-100	135	135	135	225	225	225	360	360	360
Eudragit S-100	135	225	360	135	225	360	135	225	360
HPMC	90	90	90	90	90	90	90	90	90
Lactose	525	435	300	435	345	210	300	210	75
Magnesium stearate	10	10	10	10	10	10	10	10	10
Aerosil	5	5	5	5	5	5	5	5	5

Table 7: The following table shows the acceptance criteria for flow properties of the compound according to USP

Compressibility index (%)	Flow properties	Hausner's ratio
<10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very very poor	>1.60

PRE-COMPRESSIONAL PARAMETERS:

Table 8: Powder flow properties of Montelukast sodium formulations

Powder Blend	Angle of Repose (θ)	Bulk density(ρ_b) (g/mL)	Tapped density(ρ_t) (g/mL)	Compressibility index (%)	Hausner's ratio
Core tablet	32.67 ±0.03	0.384±0.02	0.476±0.02	19.21±0.03	1.11±0.02
FI	32.82±0.01	0.400±0.01	0.434±0.01	7.92±0.02	1.12±0.04
F2	32.34±0.03	0.384±0.03	0.434±0.02	11.52±0.03	1.1±0.06
F3	29.53±0.02	0.454±0.01	0.476±0.03	8.54±0.01	1.10±0.03
F4	28.77±0.02	0.416±0.03	0.434±0.01	8.99±0.02	1.08±0.02
F5	28.77±0.03	0.454±0.04	0.476±0.04	6.89±0.03	1.08±0.01
F6	29.35±0.01	0.408±0.01	0.425±0.05	4.53±0.02	1.07±0.03
F7	29.53±0.02	0.410±0.03	0.456±0.02	4.16±0.02	1.06±0.03
F8	28.56±0.03	0.407±0.03	0.434±0.01	4.53±0.01	1.08±0.02
F9	29.21±0.08	0.412±0.10	0.443±0.06	4.08±0.04	1.09±0.04

POST COMPRESSIONAL PARAMETERS:

Table 9: Evaluation Parameters for all Formulations

Parameters / Formulations	Hardness (kg/cm^2) ± S D	Percent Friability	Weight Variation ± SD	Drug content (mg/tab) ± SD
FI	5.5±0.15	0.5	1060±0.15	99±0.25
F2	5.9±0.10	0.4	1059±0.10	98±0.98
F3	6.5±0.15	0.5	1058±0.18	97±1.67
F4	6.8±0.10	0.4	1060±0.12	99±0.25
F5	7.4±0.10	0.5	1058±0.04	97±0.98
F6	7.2±0.12	0.7	1060±0.06	99±0.65
F7	6.5±0.08	0.8	1059±0.08	98±0.54
F8	6.8±0.06	0.5	1057±0.04	97±0.78
F9	7.1±0.15	0.6	1059±0.01	98±0.85

IN VITRO DISSOLUTION STUDIES:

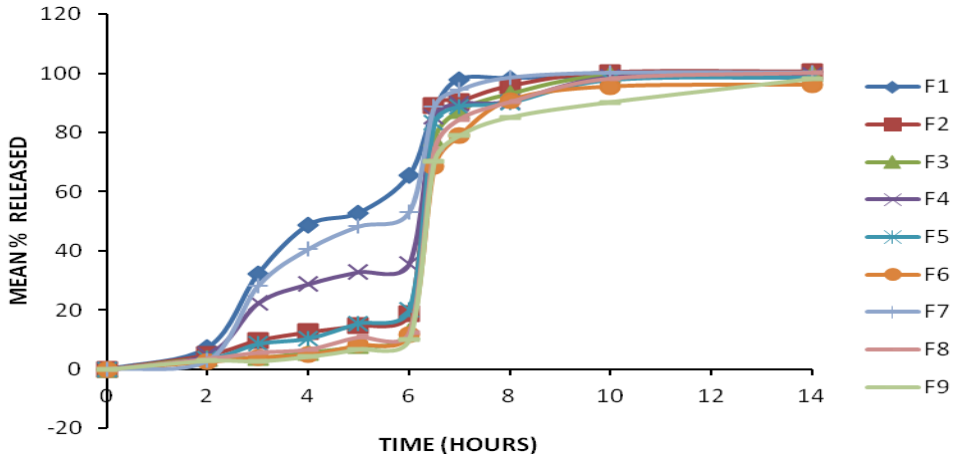


Fig.7: Dissolution profile for Montelukast sodium tablets by in situ pH change method

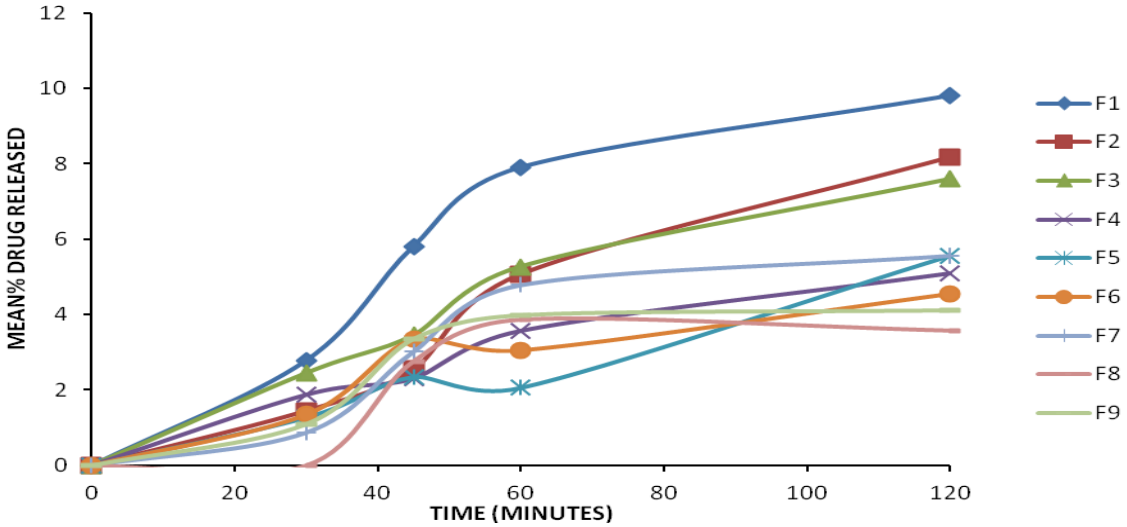


Fig 8: Dissolution profile for Montelukast sodium tablets in pH 1.2 buffer.

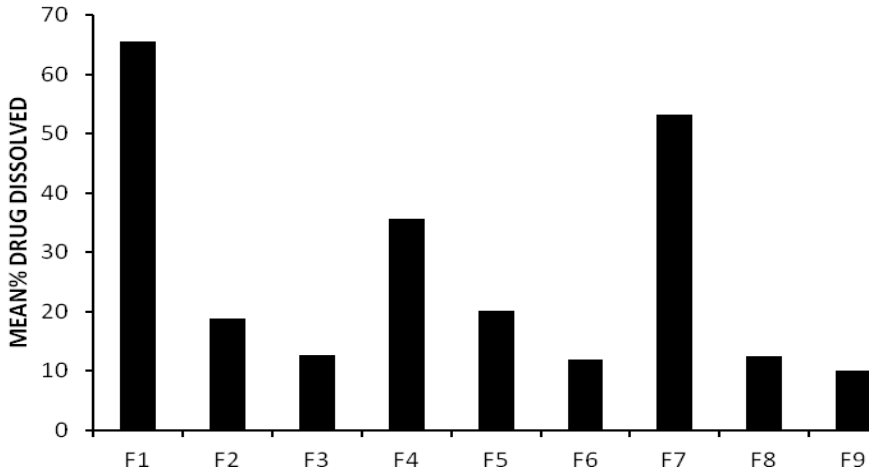


Fig.9: Effect of L-100 to S-100 ratio on release of Montelukast sodium at pH 6.8

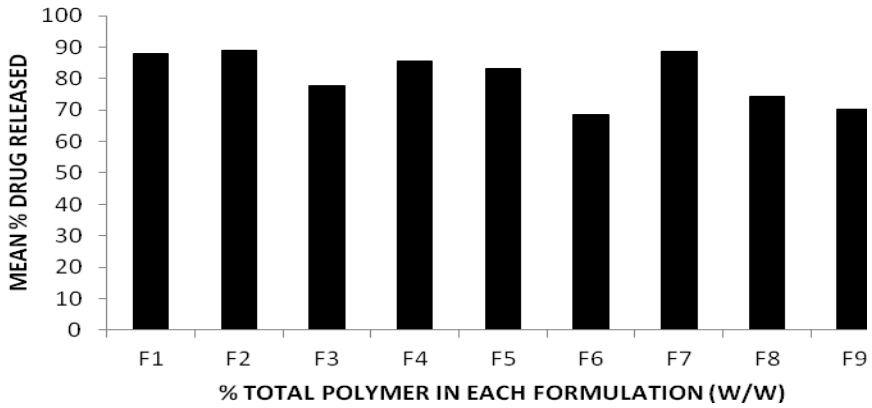


Fig.10: Effect of total polymer percent on drug release in pH7.4 at 6.5 hrs

Table 10: Cumulative Percent Drug Release of Montelukast sodium formulations

TIME(H)	CUMULATIVE PERCENT DRUG RELEASE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
2	7.5	4.88	3.79	5.01	3.5	2.57	3.06	3.57	2.86
3	32.37	9.78	3.89	22.37	8.59	4.04	28.27	5.65	2.76
4	48.78	12.56	5.76	28.78	10.43	4.89	40.64	6.72	4.25
5	52.89	14.86	7.89	32.89	15.57	8.23	48.29	10.89	6.78
6	65.6	18.87	12.64	35.69	20.08	11.86	53.17	12.47	10.13
6.5	87.98	88.98	77.89	85.47	83.29	68.54	88.76	74.38	70.28
7	97.95	90.54	87.54	89.81	88.68	78.84	94.39	84.43	78.97
8	98.32	95.68	93.27	90.54	90.09	90.87	98.54	90.28	85.15
10	99.00	100.27	99.56	98.76	97.68	95.48	100.19	98.16	90.27
14	100.37	100.58	100	99.57	98.53	96.09	100.28	100.09	98.16

Table 11: The Rate Constant and Regression values of Montelukast sodium formulations

FORMULATIONS	ZERO ORDER		FIRST ORDER		HIGUCHI	PEPPAS	
	K	R^2	K (h^{-1})	R^2	R^2 Mg/$hr^{1/2}$	'n' value	R^2
F1	8.53	0.783	0.529	0.805	0.835	0.466	0.880
F2	9.70	0.709	0.476	0.737	0.560	0.395	0.723
F3	9.83	0.710	0.495	0.684	0.521	1.079	0.851
F4	8.95	0.786	0.423	0.77	0.704	1.707	0.831
F5	9.50	0.727	0.386	0.743	0.569	0.38	0.810
F6	9.42	0.73	0.324	0.722	0.527	1.35	0.953
F7	8.87	0.786	0.520	0.799	0.787	0.349	0.853
F8	9.66	0.732	0.386	0.717	0.535	1.152	0.972
F9	9.36	0.736	0.262	0.727	0.514	1.183	0.834

CONCLUSION:

In the present study, attempt was made to develop a novel multifunctional coated mini-tablets-in-capsule system device containg immediate-release and sustain-release coated mini-tablets. The aim was to specifically target the nocturnal peak symptoms of asthma.

Prior to formulation, preformulation studies were carried out in order to establish compatibility between drug and polymers by IR spectroscopy. The results revealed that the drug and polymers were satisfactorily compatible without any significant changes in the chemical nature of the drug.

The granules of all the formulations were evaluated for pre-compressional parameters. The results revealed that all the formulations shows good pre-compressional properties showing better flowability.

Calibration curves were constructed for Montelukast sodium in pH 1.2, 6.8 and 7.4 buffers with concentration ranging from 5 - 40 µg/mL against absorbance at 332nm using UV spectrophotometer. The present analytical method obeyed Beer's law within the concentration range and plots showed good linearity indicating that the selected UV spectrophotometric method was found to suitable for the estimation of Montelukast sodium and for in vitro dissolution studies.

From the solubility studies data it was found that the drug's highly soluble in pH 7.4 buffer.
Dug excipients compatibility studies were carried out by FT-IR spectral analysis and the results revealed that there was no interaction between drug an excipients used in the investigation for the development of timed release tablets.

The pre-compressional parameters for timed release formulations i.e, Bulk density, Tapped density, Compressibility index, Hausner's ratio and Angle of repose were studied and the results were within the limits indicating that the physical mixtures of the formulations were suitable to formulate into timed release tablets.

The post compressional parameters for the formulation tablets i.e, Hardness, Friability, Drug content uniformity and Weight variation were evaluated and the results obtained were satisfactory.

In vitro drug dissolution studies were carried out in pH 1.2 for 2 hrs, pH 6.8 for 4 hrs and pH 7.4 phosphate buffer for 8 hrs respectively and based on the *in vitro* drug release profiles, formulations F1, F2, F4, F5 and F7 has passed the criteria of Q NLT < 80% within 30 minutes of exposure in pH 7.4 phosphate buffer.

The tablets F1, F2, F4, F5 and F7 released only 7.5%, 4.88%,5.01%, 3.5% and 3.06% of drug respectively in the physiological environment of stomach and small intestine and released 87.98% 88.98 %, 85.47%, 83.29% and 88.76% of the drug immediately after entering the 7.4 pH buffer in 30 minutes (at 6.5 hrs). The presence of pH sensitive polymers in the coat reduces the initial premature drug release in the upper part of GIT and ensures complete release of drug in the colon. To ascertain the mechanism of the drug release, the *in vitro* drug release data as fitted into various release kinetic models such as zero order, First order, Higuchi and Peppas models. When the first order plots were linear compared to with that of the zero order plots and the regression coefficient (r^2) obtained for the first order kinetics to indicates the drug release from

the formulations. To evaluate the drug release mechanism from the tablets, plots of percent drug released Vs square root of time as per Higuchi's equation indicating that the drug release from the tablets. To confirm the release the data was fitted into the Korsmeyer Peppas equation with 'n' value between 0.45 to 0.89 thus indicates the mechanism of drug release following Non-fickian diffusion which includes coupling of diffusion and erosion mechanism.

From the present study it can be concluded that the compressional coating was a viable method to prepare timed release Montelukast sodium tablets using pH sensitive polymers.

REFERENCES:

1. Janugade BU, Patil SV, Lade PD. Formulation and evaluation of press-coated Montelukast sodium tablets for pulsatile drug delivery system. Int. J. chem. Res. 2009; Vol 1, Issue-3: 690-695.
2. Janugade BU, Patil SS, Patil SV, Lade PD. Effect of PVP concentration on lag time of press-coated Monteleukast sodium tablet. J. Pharm. Res. March. 2009; Vol-2, Issue-3: 502-506
3. Shivkumar HN, Sarosija Suresh, Desai BG. Design and evaluation of pH sensitive mini-tablets for chronotherapeutics delivery of theophylline. Ind. J. Pharm. Sci. 2007; Issue-69, 73-79.
4. Kanakdurga Devi N, Prameela rani, Sai Mrudula B. Formulation and evaluation of oral disintegrating tablets of Montelukast sodium: Effect of functionality of superdisintegrants. J. of Pharm. Res. 2010; 3(4): 803-808.
5. Raghavendra Rao NG, Suryakar VG, Ketan Thube. Development of mucoadhesive films for buccal administration of Montelukast. J. Pharm. and Tech. March 2010; Vol-2, Issue no-1: 1-15.
6. Martindale. The complete drug reference.33rd edition, Page nos: 455-456.
7. Clark's analysis of drugs and poisons. Edited by Anthony Moffat, David M Ossceiton and Brain widdop.3rd edition, 2004, Page no: 1299-1300.
8. http://www.drug.com./cons/Montelukast.html.
9. Sampath Kumar KP, Debjit Bhowmik, Chiranjib, Margret Chandira, Tripathi KK. Innovatons in sustained release drug delivery system and its market opportunities. J. Chem. and Pharm. Res. 2010; 2(1): 349-360.
10. Rakesh Patel, Ashok Baria. Formulation development process optimization of Theophylline sustained release market tablet. Int. J. Pharm. and Pharm Sci. Oct-dec.2009; Vol-1, issue 2: 30-42.
11. Carla Lopes M, Jose Manual Souza Lobo, Jaao Pinto F, Paulo, Costa. Compressed mini-tablet as a biphasic drug delivery system. Int. J. Pharm. 2006; 323: 93-100.
12. Ying Huan Li, Jia-bi Zhu. Modulation of combined release behaviour from a novel "tablet in capsule system". J. Con. Rel; 95(2004): 381-389.
13. Mako to Ishida, Keichi Abe, Marora Hashezime. A novel approach to Sustained Pseudoephedrine release- Differentially coated nini-tablets in HPMC capsules. Int. J. Pharm. 2008; 359: 46-52.
14. Suresh H, Pathak S. Chronopharmaceutics. Emerging role of bio-rhythms in optimizing drug therapy. Ind. J. Pharm. Sci. 2005; 67(2): 135-140.
15. Smolensky MH, Peppar AN. Chronobiology drug delivery and chronopharmaceutics. Adv. Drug Del. 2007; 59: 825-851.
16. Hrashesky WIM, 1994. Timing is everything the Sci, 32-37.
17. Drelaywaja. Chronotherapeutics: Right drugs at right time can heal effectively, Healthmad. March 22 -2010. Available at http://healthmad.com
18. Korenama, Charles DP. New staratagies in the medical management of asthma. Amer. Fam. Physician. 1198, 58(1).
19. Evaluation of a hospital pharmacy based pharmaceutical care services for asthma patients. Pharmacy Practice (lnternet) V.6n.1, Redondala Jan-March.2008.
20. Zuzana Damiant, Eva Mantzouaranis, and Leif Bjermer. Montelukast in the treatment of asthma and beyond. Exp. Rev. Clinical. Immu. November 2009; Vol 5, No 6: 639-658.